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Bioorganic & Medicinal Chemistry 14 (2006) 2763–2770
Bioorganic & Medicinal Chemistry

Classification of dopamine, serotonin, and dual antagonists by decision trees

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Received 1 November 2005; revised 29 November 2005; accepted 29 November 2005
Available online 4 January 2006

Abstract—Dopamine antagonists (DA), serotonin antagonists (SA), and serotonin–dopamine dual antagonists (Dual) are being used as antipsychotics. A lot of dopamine and serotonin antagonists reveal non-selective binding affinity against these two receptors because the antagonists share structurally common features originated from conserved residues of binding site of the aminergic receptor family. Therefore, classification of dopamine and serotonin antagonists into their own receptors can be useful in the designing of selective antagonist for individual therapy of antipsychotic disorders. Data set containing 1135 dopamine antagonists (D_2, D_3, and D_4), 1251 serotonin antagonists (5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C}), and 386 serotonin–dopamine dual antagonists was collected from the MDDR database. Cerius2 descriptors were employed to develop a classification model for the 2772 compounds with antipsychotic activity. LDA (linear discriminant analysis), SIMCA (soft independent modeling of class analogy), RP (recursive partitioning), and ANN (artificial neural network) algorithms successfully classified the active class of each compound at the average 73.6% and predicted at the average 69.8%. The decision trees from RP, the best model, were generated to identify and interpret those descriptors that discriminate the active classes more easily. These classification models could be used as a virtual screening tool to predict the active class of new candidates.

1. Introduction

Traditionally, antipsychotics are considered to act via the blockade of the classical 'D_2 receptor'.[1,2] In early 1990, the discovery of dopamine D_3 and D_4 receptor, and their distribution in brain allowed us to consider a new group of antipsychotics devoid of extrapyramidal side effects.[3–5] The first atypical antipsychotics clozapine, released in February 1990 blocks not only dopamine receptor (D_2 and D_4) but also serotonin (5-HT_2), acetylcholine, α1, and H1 receptors.[6,7] The discovery that clozapine is a potent 5-HT_{2A} antagonist suggested that serotonin might be involved in the cause of schizophrenia. This led to the formulation of serotonin–dopamine antagonist (Dual) concept for antipsychotics, with wider spectrums of activity and lower extrapyramidal symptom (EPS) liability.[8–10] The principle of Dual is that the drug should be a potent serotonin 5-HT_{2A} antagonist, with a slightly less potent dopamine D_2 antagonist. However, it was proved that the selective saerotonin antagonists could be a new group of antipsychotics by themselves. The selective 5-HT_{2A} antagonist MDL 100907 has shown antipsychotic potential without specific affinity for the dopamine receptor.[11,12] Three 5-HT_2 receptor subtypes (5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C}) show considerable homology at genetic, structural, and functional levels.[13,14] Therefore, atypical antipsychotics also bind to other subtypes, 5-HT_{2B} and 5-HT_{2C}, as well as to the 5-HT_{2A} receptor subtype. More recently, human 5-HT_6 and 5-HT_7 receptors have been cloned.[15,16] Although additional studies are certainly warranted, there is some evidence to suggest that 5-HT_6 and 5-HT_7 receptors could be involved in psychosis.[17,18]

The aminergic receptors such as dopamine and serotonin receptors show highly conserved residues in their binding site, and a number of interactions of aminergic GPCRs with their ligands appear to involve similar positions in the binding site.[19] Consequently, a large number of reported antagonists exhibit non-selective binding

Keywords: Classification; Dopamine antagonist; Serotonin antagonist; Serotonin–dopamine dual antagonist; LDA; SIMCA; RP; ANN.
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doi:10.1016/j.bmc.2005.11.059

affinity for dopamine and serotonin receptors. Therefore, the identification of the comprehensive structural difference between DA and SA is a way to design selective antagonist for individual therapy. Specially, classification models for DA and SA could be merged with the subtype relevant classification model for dopamine antagonists to develop an antidepressant agent devoid of extrapyramidal symptoms via blocking D_2 receptor.[20]

For that reason, the classification models were generated to categorize and predict selective dopamine antagonists (DA), selective serotonin antagonists (SA), and serotonin–dopamine dual antagonists (Dual) with antipsychotic activities. Classification methods including linear discriminant analysis (LDA),[21] soft independent modeling by class analogy (SIMCA),[22] recursive partitioning (RP),[23] and artificial neural networks (ANN)[24] were applied to analyze the structure–activity relationship using 2-dimensional molecular structural descriptors implemented by Cerius2.[25] In this paper, we report that the classification models for antipsychotics consist of various scaffolds and compare with the results obtained with four different classification methods. Finally, we generate a decision tree for our best model, RP, and report the description for decisive factors.

2. Methods

2.1. Data set and descriptors

The antagonists of different types of receptors from the MDDR[26] database were collected for data set as shown in Table 1. The antagonists for 5-HT_6 and 5-HT_7 receptors have not been found in the MDDR. Each receptor ligand was assigned a receptor classification (DA = 1, SA = 2, or Dual = 3). Counterions and solvent molecules were eliminated and charged groups were neutralized by the addition or removal of protons. Duplicates within and between the classes were removed. The SD file corresponding to all the data set molecules was loaded into a Cerius2 study table. All structural, topological descriptors, and A log *P*98 were calculated as initial descriptor set.[25] Descriptors with constant values as well as descriptors containing 95% zero values were removed. The correlation matrices of descriptors were built and some descriptors were deleted on the basis of the correlation threshold of $R = 0.9$. Finally, total 22 descriptors were obtained as shown in Table 2 and used as independent variables (X) in all the analyses.

All data set was divided into two subgroups: the training and test sets. The training set consists of 90% of the total data and the test set 10% of the total data. The test compounds were selected equally from each subtype of receptors.

Table 1. The number of data sets collected from the MDDR

	Class	Number of compound
1	Selective dopamine antagonists	1135 (D_2: 260, D_3: 263, D_4: 612)
2	Selective serotonin antagonists	1251 (1A: 517, 2A: 447, 2C: 287)
3	Serotonin–dopamine antagonists	386

Table 2. Descriptors used to develop classification models

Descriptor	Information
Balaban indices[28] (1)	The shape of a molecule
CHI indices[29] (5)	Molecular connectivity
E_state_keys[30] (12)	The electrotopological interaction for each atom
Log Z[31] (1)	The degree of branching
Wiener[32] (1)	The length of chemical bonds existing between all pairs of heavy atoms
Structural descriptor (2)	The number of H-bond donors and acceptor

2.2. LDA model development

Linear discriminant analysis (LDA)[21] was carried out by Cerius2 implementation. LDA calculates a set of orthogonal basis vectors using an identified sample. These orthogonal basis vectors maximize the separation of means between categories and minimize the variances within categories. These vectors or discriminant functions act as axes to plot the data in n-dimensional descriptor space. LDA then classifies unknown samples by their standardized distances from the means of the categories. The number of components was determined three using all variables.

2.3. SIMCA model development

The SIMCA algorithm[22] is similar to the LDA, except that it applies the principal component analysis (PCA) separately to each class of objects instead of just one model for all samples and uses the principal components (PCs) to define hyper-volumes in descriptor space. The SYBYL[27] implementation was used to generate a SIMCA model. Prediction consists of calculating the distance to the hyper-volume for each category. The number of significant components was calculated with pre-scaled descriptors in a 4-fold cross-validation procedure. The optimal number of components for each category was selected based on the sum of squared residuals for each compound.

2.4. RP model development

The RP method was performed using the CART algorithm implemented in Cerius2.[25] The RP method categorizes objects by deriving a binary decision tree in which descriptors are used to split the data set into smaller, homogeneous subsets. The activity classes were weighted equally, and the splits were scored using the Gini Impurity scoring function. The pruning factor values were varied between 3 and 6. The value of 1/100 of samples was considered as the minimum number of samples in any node. The various values were used for the maximum tree depth (layers <10) and the default values were accepted for the maximum number of generic splits (30) and the number of knots per variable (20).

2.5. ANN model development

A fully connected, three layer-backpropagation neural network (BPNN) was trained using the Cerius2 program.[24] The network tries to minimize errors between the estimated classes and the true classes. Each descriptor set was submitted to ANN input signals for the input neurons. The number of hidden layer neurons was varied to find out the best classification model. The best model was determined by trial and error. The optimum four hidden layer was selected for the model.

3. Results and discussion

3.1. Development of classification model

For the training set consisting of 2496 antagonists, all models presented a good recognition rate that total correct percent ranged from 65.8% to 79.9% (Table 3). The classification accomplished by ANN showed the best result among the models derived using four different methods, the recognition rate for DA, SA, and Dual with 77.3%, 83.1%, and 77.3%, respectively. The RP model also demonstrated a considerably good recognition rate of 77.5%. LDA achieved satisfactory classification with a total recognition rate of 71.3%. The SIMCA algorithm illustrated a slightly lower 65.8% correct recognition rate than that obtained with the LDA. The classification techniques yielded an average correct percent of 73.4 and 72.1 for DA and SA, respectively. Although the number of Dual was relatively smaller than those of other two classes, the average classification rate was nearly 80% in the four different classification models. Actually, many known DA or SA may have dual activities because anyother biological activity was not measured in these compounds. This noise in the data set may influence the decrease of the recognition rate and it may be the reason why Dual had a better recognition rate than DA and SA. All classification models by 22 of 2D structure-based descriptors successfully categorized three classes of dopamine and serotonin antagonists. These results provided the proof that our descriptor set is able to describe the structural difference of receptor selectivity.

Table 3. Classification results for dopamine antagonist, serotonin antagonist, and serotonin–dopamine dual antagonist

Method	Training (%)			Total recognition/2496 (%)
	DA/1022	SA/1126	Dual/348	
LDA	745 (72.9)	768 (68.2)	267 (76.7)	1780 (71.3)
SIMCA	690 (67.5)	677 (60.1)	275 (79.0)	1642 (65.8)
RP	775 (75.8)	867 (77.0)	293 (84.2)	1935 (77.5)
ANN	790 (77.3)	936 (83.1)	269 (77.3)	1995 (79.9)
	Prediction (%)			Total prediction/276 (%)
	DA/113	SA/125	Dual/38	
LDA	82 (72.6)	86 (68.8)	24 (63.2)	192 (69.6)
SIMCA	74 (65.5)	74 (59.2)	27 (71.1)	175 (63.4)
RP	83 (73.5)	93 (74.4)	29 (76.3)	205 (74.3)
ANN	81 (71.7)	90 (72.0)	27 (71.1)	198 (71.7)

To verify our classification models, the prediction test was checked using an external test set that was selected randomly. Table 3 shows good predictive potentials by all the models. The LDA model predicted correctly about 70% of the test set and the SIMCA model generated a moderate predictability of 63.4%. The ANN and RP models predicted the test set with a success rate greater than 70%. These are important results as they indicate that the used descriptors are powerful tools to predict the pharmacologically active class of candidates for an antipsychotic agent. The ANN has executed the best classification in the training set, but the predictability for the test set was slightly lower than the RP results. The RP model produced the best prediction results of 74.3%. Therefore, we have focused our attention on the generation of RP trees.

3.2. Generation of RP trees

The variation of the pruning factor was investigated at default parameters as described earlier and maximum tree depth = 10. Although the complexity of the decision tree reflects high similarity in the structure of three classes of antagonists, the RP tree obtained at a pruning factor of 3 was generally very complex and difficult to determine the decisive factor to be important. To build a simplified tree that is likely to be useful in predicting the activity, the variation of the pruning factor was investigated to be between 3 and 6 at the interval of 0.5. The minimum sample size was retained 1/100 in all these investigations, and the rest of the parameters were set to a default value as described earlier. Table 4 reports the true positive rates for each class in terminal nodes. The optimum tree that was simpler and hence more desirable to use in prediction was determined by pruning factor = 5. The variation of maximum tree depths was also investigated at a pruning factor of 5 and default parameters as described earlier. Figure 1 shows the relationship between the number of tree depths and prediction rate for training and test sets. The correct recognition rate of training set is being increased but the best prediction rate of test set is recorded at the tree depth 8. Therefore, the maximum tree depth, 8, was determined as the optimal value. To reconfirm the validity of the determined pruning factor, we checked the classification rate of training and test sets. Figure 2 displays the classification rate by various

Table 4. True positive rate of predicted hits for each class of antagonist as a function of the pruning factor (α)

Pruning factor	Correct classification rate (%)		
	DA	SA	Dual
3.0	60.9	60.7	65.4
3.5	66.1	66.8	72.7
4.0	67.5	74.2	77.4
4.5	74.6	76.1	80.6
5.0	77.2	79.4	85.6
5.5	72.3	74.9	81.3
6.0	68.9	73.0	79.5

All rates obtained with the maximum tree depth = 10, minimum sample size 1/100 samples, and other default parameters.

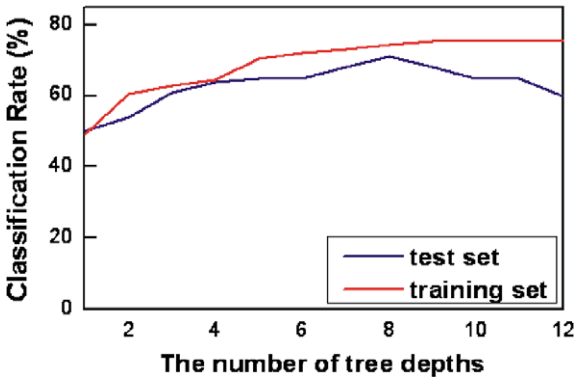


Figure 1. The prediction rates of the best model by recursive partition with different number of maximum tree depths at the pruning factor of 5. The training and test sets are colored red and blue, respectively. The best tree depth was determined based on the predictive value of test set.

pruning factors at the maximum tree depth 8. The classification rate of training was very much similar to the classification obtained with the maximum tree 10.

3.3. Description of decision trees

Figure 3 displays the recursive partitioning decision tree by the encouraged descriptors to classify three active classes. The red color indicates dopamine antagonists, the green color means serotonin antagonists, and the serotonin–dopamine dual antagonists are plotted using dark gray color.

Table 5 reports the description and illustration of decision factors that were found to be important. One of the key descriptors of our RP tree is electrotopological value (E-state key) computed for each atom in a molecule and which encodes information about both the topological environment of that atom and the electronic interactions due to all other atoms in the molecule. That is, the information of the electron accessibility at that atom and the degree of adjacency or topological state of the atom were provided by the E-state key. The meaning of the E-state symbols in Cerius2 implementation is as follows: *S*, sum of the numerical value for the following atom type; s, single bond; d, double bond; t, triple bond; a, aromatic bond.

The E-state key, S_ssCH$_2$, is the first decisive factor for discrimination between SA and Dual, and stands for the sum of intrinsic values for the –CH$_2$ atom type with two single bonds. The three-ordered connectivity index (CHI-3), which provides information of the overall shape in a molecule, followed as the second descriptor to classify SA and DA. It was found that several SA and Dual have different electrotopological environments for aromatic carbon and ester atom types. These splits provide the information that some of the SA have a relatively lower availability of the aromatic atom for intermolecular interaction and a smaller degree of adjacency to the aromatic atom type compared to a part of Dual. In contrast to this, the electron accessibility at an ester atom type is higher in some SA classes rather than in Dual and the degree of adjacency is relatively lower. Hence, the main structural difference between SA and Dual could be summarized by the availability of alkyl chains when an antagonist binds to the receptor, the overall shape of a molecule, and the difference of electrotopological environment around aromatic and ester atom types among those antagonists.

To characterize the structural difference between DA and Dual, the number of hydrogen donors is one of the important descriptors. It is because the hydrogen bond donor atom is not involved in the structure of most Dual antagonists. The valence-modified first order connectivity descriptor (CHI-V-1) encodes the information for the number of edges in a molecular graph. The electrotopological descriptors for amine and ester atom types also divided the DA and Dual with a molecular shape-related descriptor, CHI. Wiener index, which expresses the length of chemical bonds existing between all pairs of heavy atoms, contributed to separating the DA from the Dual class. As these results, the major structural difference between DA and Dual was decided on the number of hydrogen bonding,

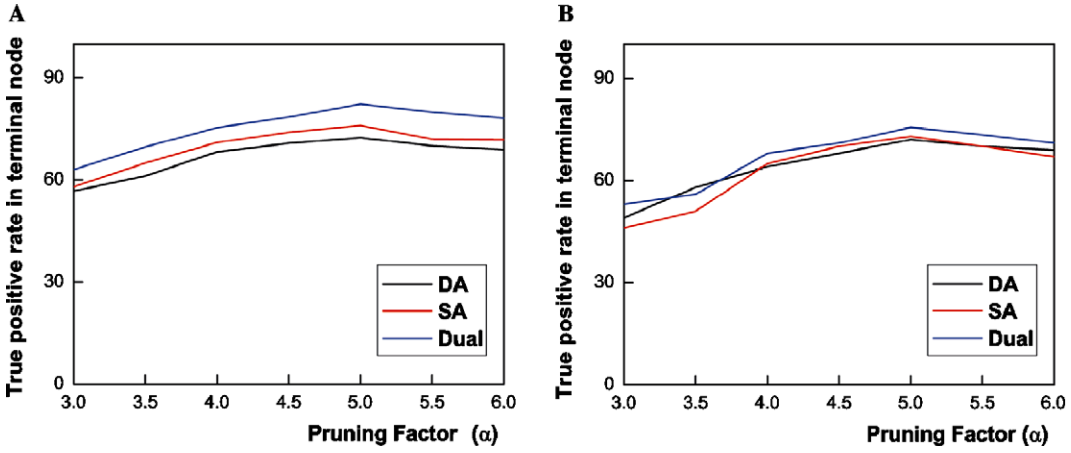


Figure 2. True positive rate of predicted hits for each class of antagonist as a function of the pruning factor (α). (A) Training set. (B) Test set. The maximum sample size was set to 1/100 and the maximum tree depth was retained as 10 in all these trials. The default values were used for all other parameters.

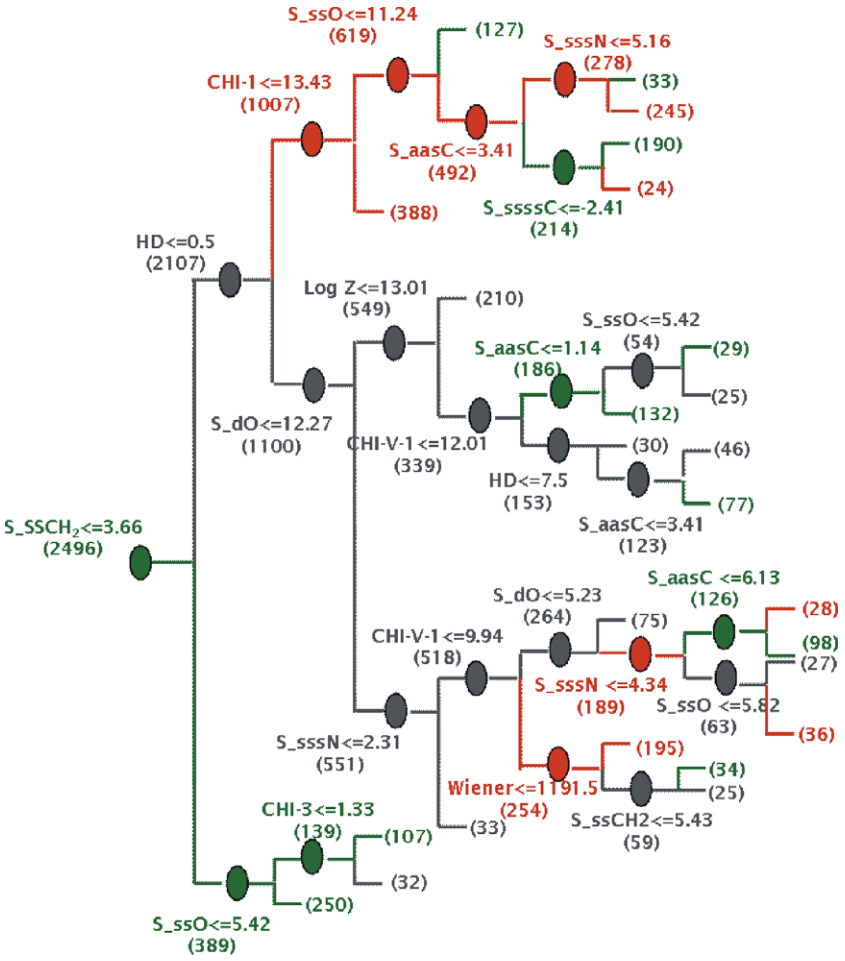
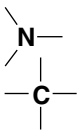


Figure 3. RP tree generated with moderate pruning factor (5) and 8 maximum tree depth. The red color indicates dopamine antagonists, the green color means serotonin antagonists, and the serotonin–dopamine dual antagonists are plotted using dark gray color.

Table 5. Summary definition of all descriptors that were found to be important by a decision tree with the best predictive ability

Index	Description	Illustration
S_ssCH$_2$	Sum of the atom level E-state values for all the group, –CH$_2$, in the molecule	
S_ssO	Sum of the atom level E-state values for all ester groups in the molecule	
S_aasC	Sum of the atom level E-state values for all the carbon with two aromatic and one single bond in the molecule	
S_dO	Sum of the atom level E-state values for all oxygen atoms with one double bond in the molecule.	R = O
S_sssN	Sum of the atom level E-state values for all nitrogen atoms with three single bonds in the molecule	
S_ssssC	Sum of the atom level E-state values for all the carbon with four single bonds in the molecule	
CHI-1	Molecular shape descriptor, encodes the information for the number of edges in a molecular graph	
CHI-V-1	The valence-modified first order connectivity descriptor	
CHI-3	Molecular shape descriptor, encodes the overall shape of the molecule	
HD	The number of hydrogen bonds	
Log Z	The degree of branching of the molecule	
Weiner	The length of chemical bonds existing between all pairs of heavy atoms	

the size of a molecule, the distribution of heteroatoms of each molecule, and the availability for amine and ester atom types of an antagonist in interaction with receptor.

The classes of DA and SA could be differentiated with the correct recognition rate to be more than 75% using the descriptors that encoded the information of the electron accessibility for aromatic carbon,

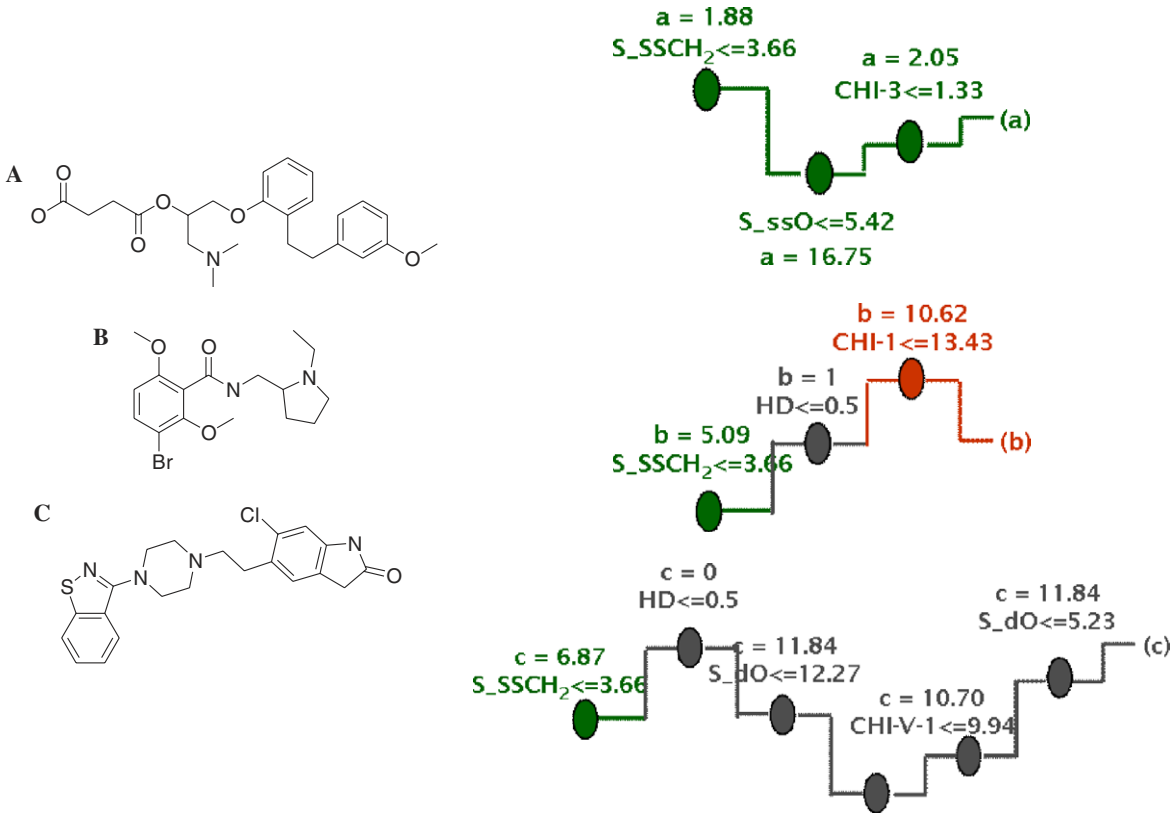


Figure 4. The typical compounds in each class and descriptor values used to correctly classify them in our decision tree. The decision trees are the parts of our entire decision tree. (A) SA: Sarpogrelate, 5-HT_{2A} antagonist. (B) DA: Remoxipride, dopamine D_2 antagonist. (C) Dual: Ziprasidone, 5-HT_{2A} antagonist and dopamine D_2 antagonist.

ester, amine atom types, and alkyl chain in intermolecular interaction.

It is not so easy to describe the exact structural feature of the compounds in a specific class, because most of the classification models are built with a structurally diverse compound set. Thus, we show the typical compounds in each class. Figure 4 provides how to classify the typical compounds into the specific node according to their structural properties. Each launched compound is successfully classified into its class by a part of decision tree.

Our purpose was to find meaningful descriptors to differentiate DA, SA, and Dual. To solve this problem, we employed 22 structure-based descriptors. The remarkable two descriptors, E-state and CHI value, encode the information of the electron accessibility for an atom and the information for the shape of a molecule, respectively. In this sense, the E-state values encode the potential for non-covalent intermolecular interaction. The CHI descriptors encode the profile of complementariness between drug and receptor. Although the structure of identified DA and SA is almost similar, the classification by the above descriptors produced considerable discriminative power in the training set. Moreover, the prediction test by the RP tree resulted in a 71% prediction rate.

For these reasons, we could conclude that understandable descriptors connected with drug–receptor encoun-

Table 6. Mean values and standard deviations of classification obtained in ten different training and test sets

	Class	LDA	SIMCA	RP	ANN
Training set	DA	73.6 ± 0.2	64.5 ± 3.8	74.8 ± 2.8	76.7 ± 1.4
	SA	69.4 ± 0.4	63.2 ± 1.4	75.0 ± 3.4	82.2 ± 1.5
	Dual	77.6 ± 0.3	77.5 ± 1.2	82.5 ± 2.4	80.4 ± 2.9
Prediction test	DA	73.5 ± 0.4	63.5 ± 3.6	71.0 ± 5.3	68.7 ± 3.4
	SA	68.2 ± 0.3	56.2 ± 2.4	69.5 ± 6.9	69.8 ± 3.2
	Dual	62.7 ± 0.5	68.7 ± 3.2	71.9 ± 8.7	67.3 ± 6.0

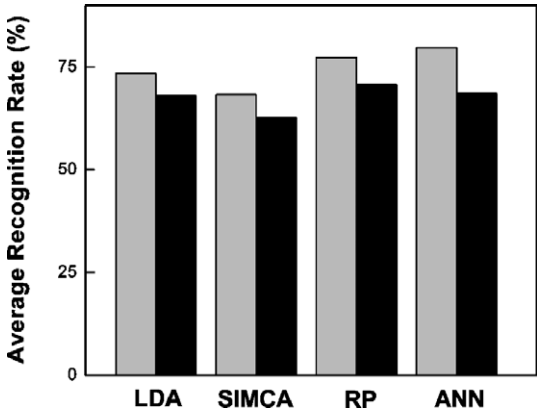


Figure 5. The total average prediction rates for training (gray) and test sets (black). The ANN model gave the best recognition rate and the RP model generated the best predictive power.

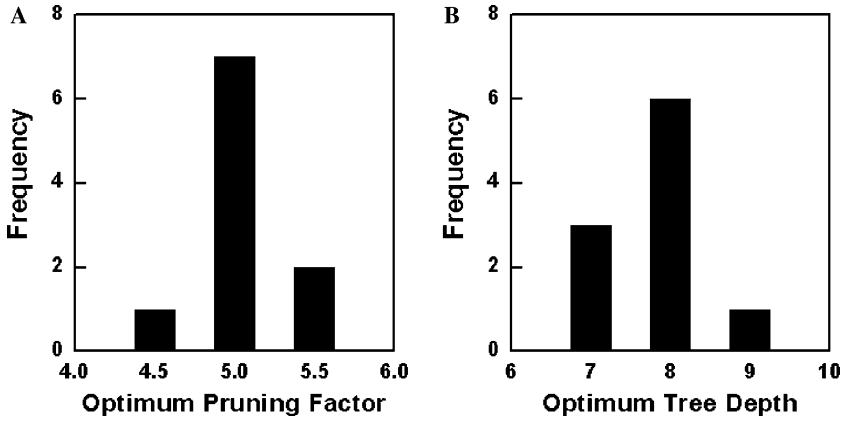


Figure 6. The distribution of optimum pruning factor and optimum tree depth in RP trees with ten training sets. The best model of the RP tree was generated with pruning factor (5) and 8 maximum tree depth.

ters were identified for our goal. The identified distinctive structural aspects for DA and SA could be used to predict the target class of new antipsychotic candidates in the preliminary step of drug discovery. Since our model employs diverse training molecules, it should be useful in evaluating new compounds.

3.4. Model validation by cross-validation test

To avoid overfitting and to improve generalization of the classification models, ten different trial data sets were validated. For the total set containing both the training set and test set, 10 different trial data sets were divided randomly. Each trial data set was used as the prediction set, and the remaining data sets were employed to derive models. The average and standard deviation results of ten different trials are summarized in Table 6. The training sets achieved acceptable correct recognition percent and the test sets also showed a reasonably good predictability. Figure 5 displays the average correct classification rate and prediction rates of all models. The RP algorithm gave the best prediction rate and the SIMCA method showed the least classification rate. To validate the robustness of our decision tree, we also investigated the consistency of descriptors that were found to be important in ten trainings. The key descriptors on the decision tree generated in the ten training processes were relatively consistent with decisive factors of the best model. All generated decision trees also exhibited the stability for the optimum pruning factor and the optimum number of tree depths. Figure 6 shows the distribution of the optimum pruning factor and the tree depth in ten training processes. The predictive accuracies of the classification algorithms prove that our models are valid to classify and predict the active class of new candidates. All models gave sufficient predictability to use as the virtual screening tool that the consensus-active class candidates could be screened.

4. Conclusions

The aim of the present study was to develop a discriminative model to predict receptor selective antagonists. In this study, we have calculated the topological descriptors encoding important structural characteristics that are useful for analyzing the receptor–ligand interaction. The LDA, SIMCA, RP, and ANN algorithms have been employed and compared to classify dopamine antagonists, serotonin antagonists, and dopamine–serotonin dual antagonists with antipsychotic activity. The predictabilities of our classification models were validated using external test set and cross-validation test. The RP method gave the best prediction rate among the four different methods. The recursive partitioning tree was generated with the key descriptors and these descriptors to classify the antagonists of different types of receptors were reasonably described with visual splits. These models could be used to recognize the newly considered structural pattern and to predict the active class of compounds to be obtained. Our class-based approach to the classification model provided a relatively simple performance compared to classical QSAR. The interesting candidates can be tested together as a single procedure and as a consensus scoring of four different algorithms. Therefore, the earlier identification of the activity class for the target receptor could be of assistance to the discovery of cost-effective receptor selective antagonists.

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